Sialylation Accumulates in Cancer Tissues and Promotes Development

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The tumor microenvironment (TME), where the tumor cells incite the surrounding normal cells to create an immune suppressive environment, reduces the effectiveness of immune responses during cancer development. Sialylation, a type of glycosylation that occurs on cell surface proteins, lipids, and glycoRNAs, is known to accumulate in tumors and acts as a “cloak” to help tumor cells evade immunological surveillance. The role of sialylation in tumor proliferation and metastasis has become increasingly evident. With the advent of single-cell and spatial sequencing technologies, more research is being conducted to understand the effects of sialylation on immunity regulation.

sialylation Siglecs immune checkpoint

1. Typical Sialylated Glycans in Tumors

Cancer cells are cloaked by a plethora of glycosylation, with many of them exhibiting a high level of sialylation. Glycosylation has the potential to mask essential antigenic and receptor-binding sites, as well as interact with certain checkpoints, enabling cells to avoid being recognized by enemy-identifying signals [1][2]. In addition to physical shielding, certain glycan structures possess specific physiological functions; they can act as ligands to mediate signal recognition and immune suppression [3]. These glycans comprise sialyl-Tn (STn), sialyl-T (ST), disialyl-T, sialyl-Lewis antigens, polysialic acid, and gangliosides (**Figure 1**). The broad distribution and advantageous effects on cancer cells have rendered sialylated glycans a hallmark of cancer [4].

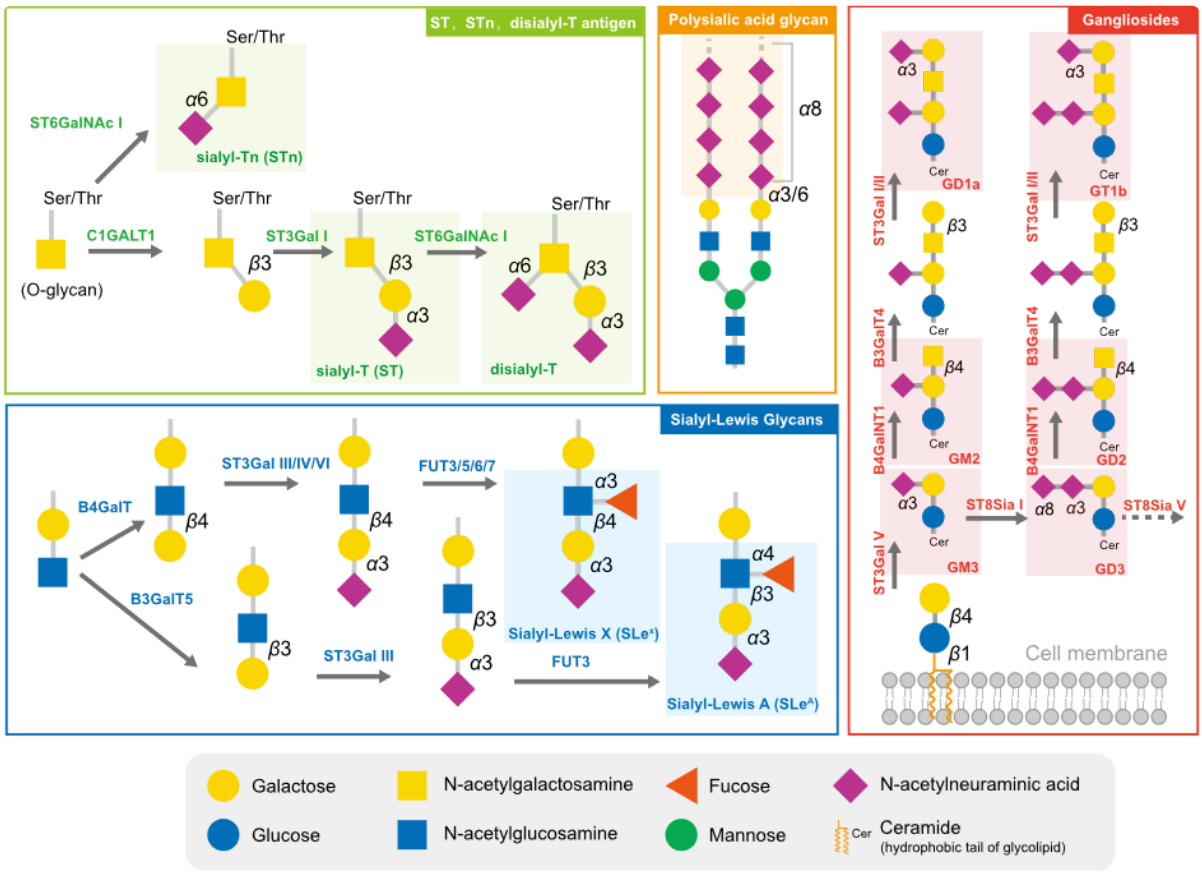

Figure 1. The typical sialylated glycans in tumors. The sialylated glycan structures typically highly expressed in tumors are marked with the translucent rectangular box.

The short sialylated O-glycan STn and ST antigens are aberrantly expressed in several cancers, with high levels being mainly observed in carcinomas and associated with aggressive tumors, such as those with chemotherapy resistance and poor prognosis [5][6]. The increased level of STn in tumor cells is primarily attributed to the upregulation of ppGalNAcT and ST6GalNAc I, combined with the low efficiency of COSMC, which assists C1GALT1 in extending glycans [6]. High serum concentrations of STn have been observed in patients with breast cancer [5], prostate cancer [6], bladder cancer [7], cervical cancer [8], and ovarian cancers and correlated to tumor grade and metastasis [9]. Due to the high prevalence of STn antigen expression in tumors, serum STn levels can be clinically utilized to assist with tumor diagnosis. ST antigens were also elevated in cancer, and the silencing of *ST3GAL1* significantly reduced the level of these antigens, further reducing the tumor size in the prostate cancer xenograft mouse model [10].

Sialyl-Lewis (SLe) antigens, SLe^A and SLe^X, are other typical structures of sialyl glycans and act as ligands for selectins, a family of lectins involved in lymphocyte trafficking. Cancer cells that are disguised by SLe^A and SLe^X are mistaken for leucocytes during their epithelial–mesenchymal transition and travel throughout the circulation system [11]. E-selectins, the primary receptors of SLe^A and SLe^X, are adhesion molecules required for leukocyte recruitment during the early stages of inflammation. The accumulation of SLe^A and SLe^X leads to cell adhesion and subsequent trans endothelial migration of traveling tumor cells. In ovarian tumors, mucins MUC16 and MUC1 are major carriers of SLe^A and SLe^x and are used as biomarkers [12].

Polysialic acid is a polymer of sialic acid, with α2,8 and α2,9 linkages and a length ranging from 8 to 400 units. It is a crucial glycosylation type for several essential proteins, providing them with a negative charge. In mammalian cells, three sialyltransferases (ST8Sia II, ST8Sia III, and ST8Sia IV) are responsible for the extension of polysialic acid glycans [13]. Polysialic acid is often detected in brain tissues and is also found in immune cells. Several molecules are found to undergo polysialylation, such as neural cell adhesion molecules (NCAMs) [14][15], chemokine receptor 7 (CCR7) [16][17], CD36 [18], and E-selectin ligand 1 (ESL-1) [19]. Interestingly, the sialyltransferase ST8Sia II and ST8Sia III can polysialylate independently. These polysialylated glycoproteins participate in physiological processes, including cell adhesion between cells and cells with a matrix, cell migration, synapse formation, and the functional plasticity of the developing nervous system. In tumor cells, the level of polysialic acid chains correlates with an aggressive phenotype and the resistance of cancer treatment [20].

Glycolipids, molecules composed of one or more carbohydrate residues linked to a hydrophobic lipid moiety via a β-glycosidic linkage, are mainly found in lipid rafts on the outer leaflet of the plasma membrane bilayer. Some gangliosides (GD2, GD3, GM2, GM3, fucosyl-GM1) are distinguishable from other gangliosides via their significantly lower or absent expression in normal cells, yet they are highly expressed in tumor cells [21]. GD3 and GD2 are highly expressed in certain tumors and can be utilized as targets for immunotherapy. However, they can also inhibit the function of immune cells, such as macrophages, via binding to Siglec-7 [22].

2. Sialyltransferases Are Critical Enzymes for Hypersialylation

Approximately twenty sialyltransferases are involved in the positive regulation of human cell sialylation, and these sialyltransferases are classified into four types based on the differences in their substrate structure and the linkage of the formed sialylation: ST3Gal I-VI (add Neu5Ac to galactose in an α2,3 linkage); ST6Gal I-II (add Neu5Ac to galactose in an α2,6 linkage); ST6GalNAc I-VI (add Neu5Ac to GalNAc in an α2,6 linkage); and ST8Sia I-VI (add Neu5Ac to Neu5Ac in an α2,8 or α2,9 linkage) [23]. The increased modification of sialic acid in various malignant tumors is caused by the high expression of sialyltransferases. Hypersialylation in the tumor microenvironment alters its physiological characteristics, blocking some immunological recognition and communication [24]. More importantly, sialylation also promotes tumor cell survival and drug resistance, as well as suppressing surrounding immune cells, which helps tumor cells to survive [25].

The sialyltransferase ST6Gal I is a well-studied enzyme, catalyzing the addition of Neu5Ac to galactose residues of Gal β1-4 GlcNAc in an α2,6 bond mainly on N-glycans. Elevated levels of ST6Gal I have been linked to a number of different cancer types and can be a driver of malignant progression, as well as resistance to therapy [26][27][28][29][30][31][32]. This is further supported by the pancreas-specific genetic deletion of *ST6GAL1* in a mouse model, which delays cancer formation [33]. Additionally, ST6Gal I has been observed to add sialylation in cell surface receptors, such as PDGFRB [27], EGFR [34][35], and PECAM [36], which increases protein levels and phosphorylation to stimulate pathways such as PI3K/AKT and RAS [26], thus contributing to tumor growth. ST6Gal I has also been implicated in the immune evasion in hepatocarcinoma cells, where it increases levels of MMP9 and suppresses T-cell proliferation [37]. Moreover, ST6Gal I is released into the extracellular milieu in either exosome or free forms,

thereby remodeling cell surface and secreted glycans, which has been linked to aggressive tumor cell proliferation in breast cancer [38]. ST6Gal II is another enzyme that can add α2,6-linked sialic acid to N-glycans. Nonetheless, this enzyme is predominately expressed in the embryonic and perinatal stages of brain tissue [39]. In a recent study of breast cancer, ST6Gal II accumulated in tumor tissue and was associated with tumor malignancy. The inhibition of ST6Gal II caused the downregulation of cell adhesion and invasion-associated proteins, resulting in reduced tumor migration [40]. Similarly, silencing *ST6GAL2* in a follicular thyroid carcinoma reduced tumor growth by inactivating the Hippo pathway in an in vivo model [41].

The ST3Gal family, consisting of six members (ST3Gal I-VI), facilitates the transfer of sialic acid to the terminal galactose residues of glycochains via an α2,3-linkage in both glycoproteins and glycolipids. ST3Gal I, which predominantly functions in core-1 O-glycans, catalyzes the transfer of Neu5Ac to a galactose residue in an α2,3 bond to produce sialyl-T antigen. The upregulation of ST3Gal I has been reported in many malignant tissues, such as ovarian cancer [42], glioblastoma tumors [43], and melanomas [44], and it has been associated with tumorigenesis, poor clinical outcomes and an inflammatory phenotype. Additionally, CD55, an essential immune checkpoint molecule, has been reported to be O-glycosylated by ST3Gal I to help cancer cells escape immune attack [45].

ST3Gal II, in contrast, prefers gangliosides as its substrate to form GD1a and GT1b [46][47]. The elevated expression of ST3Gal II has been associated with advanced stages of cancer and poor clinical outcomes. In addition, ST3Gal II is the only enzyme responsible for synthesizing the glycosphingolipid SSEA4, a well-known biomarker of several cancers [48][49]. Furthermore, *ST3GAL2* knockdown led to a dramatic growth reduction in colorectal cancer in xenografted mice models [50].

ST3Gal III, ST3Gal IV, and ST3Gal VI are implicated in the formation of SLe^A and SLe^X glycans on the cell surface, which act as binding ligands for selectins and are essential for metastasis [51][52]. The high expression of ST3Gal III has a strong positive correlation with poor prognosis in gastric cancer [53], and ST3Gal IV is the main enzyme for generating ligands of Siglec-7 and -9 [54][55]. ST3Gal VI generates selectin ligands and accumulates in liver and urinary bladder cancers [56][57]. Moreover, *ST3GAL5* encodes GM3 synthase, the rate-limiting enzyme for the production of downstream gangliosides, and is, therefore, crucial to gangliosides synthesis [46]. In renal cell carcinoma research, *ST3GAL5* was consistently overexpressed in tumor tissue and correlated with the infiltration of exhausted $CD8^+$ T cells, indicating that ST3Gal V contributes to immune suppression [58].

The ST6GalNAc family, consisting of six members, ST6GalNAc I-VI, catalyzes the α2,6 glycosidic linkage of Neu5Ac to the GalNAc residues on O-glycans or glycolipids. ST6GalNAc I, which adds Neu5Ac to O-linked GalNAc residues to form sialyl-Tn (STn), is particularly significant [59]. Evidence suggests that the overexpression of STn is associated with poor clinical prognosis in a wide range of cancer types [9][60], making it a well-known tumor-associated carbohydrate antigen. One functional study found that ST6GalNAc I can promote tumor growth and metastasis and is related to cancer cell stemness [61]. Furthermore, cytokines such as IL-13 promote the phosphorylation of STAT6, which, in turn, activates the transcription of *ST6GALNAC1*, thereby facilitating the

formation of STn [62]. The STn inhibits T-cell responses by binding to Siglec-15, leading to immune evasion in the tumor microenvironment [63][64].

ST6GalNAc II is an enzyme responsible for synthesizing ST and STn antigens. The role of ST6GalNAc II in tumors varies with the stage and status of the tumor. In breast cancer metastasis, ST6GalNAc II catalyzes the formation of ST and STn that blocks tumor binding to galectin, negatively affecting tumor metastasis [65][66]. However, in the tumor microenvironment, ST6GalNAc II is positively correlated with higher tumor stage and worse prognosis [67].

Another ST6GalNAc family member for O-glycan is ST6GalNAc IV, a key ST6GalNAc enzyme that is involved in the formation of disialyl-T antigen and GD1α from sialyl-lactotetraosyl-ceramide GM1b (gangliosides). In a primary lung cancer model, the upregulation of *ST6GALNAC4* was demonstrated to confer glycosylation changes in tumor cells, contributing to their metastatic activity. This is likely due to the preservation of the T-antigen presentation and adherence to galectin 3 [68]. The catalytic product of ST6GalNAc IV, the disialyl-T antigen, was shown to be a ligand for Siglec-7. The high expression of ST6GalNAc IV increased disialyl-T antigens in CD162 and CD45 and inhibited NK cell activity via the binding of Siglec-7 in chronic lymphocytic leukemia B cells [69]. Moreover, in liver cancer, the elevated *ST6GALNAC4* promoted tumor proliferation, migration and invasion ability, and affected the expression of immune checkpoints on tumor cells [70].

The sialyltransferases ST6GalNAc III, ST6GalNAc V, and ST6GalNAc VI are mainly involved in glycolipid synthesis. ST6GalNAc III and ST6GalNAc V use GM1b as a substrate to synthesize GD1α [71][72], whereas ST6GalNAc VI catalyzes the synthesis of α-series gangliosides, including GD1α, GT1aα, and GQ1bα; globo-series glycosphingolipids (GSL); and disialyl Le^A. It has been reported that ST6GalNAc III increased M2 macrophages via the accumulation of prostaglandin and arachidonic acid in gastric cancer [73]. *ST6GALNAC5* was expressed at low levels in tumors, and its overexpression significantly inhibited tumor growth and invasiveness [74]. On the other hand, the downregulation of *ST6GALNAC6* resulted in a change from disialyl Le^A to sialyl Le^A and an elevation in E-selectin binding activity during metastasis, which supports inflammation-driven carcinogenesis by reducing its binding to the immunoregulatory Siglec-7 [75].

Members of the ST8Sia family catalyze the transfer of sialic acid to another sialic acid, forming α2,8 linkages. Notably, the 2,8-disialic glycan structure, ligands for Siglec-7 and Siglec-9, can potentially regulate immune responses. Notably, ST8Sia I, also known as GD3 synthase, is positively correlated with the astrocytoma grade and accumulates in glioblastomas [76]. Similarly, ST8Sia II and ST8Sia IV are polysialyltransferases that produce polysialylated cell adhesion molecules, which are highly expressed during cancer development. In tumors, the expression of *ST8SIA2* has been shown to correlate with the tumor stage [77]. Moreover, the overexpression of *ST8SIA2* increased the invasiveness and metastatic abilities of small-cell lung cancer cells in vitro [77][78]. Additionally, *ST8SIA4* is overexpressed in breast cancer tissues and contributes to chemoresistance in acute myeloid leukemia [79][80]. Furthermore, ST8Sia III, which causes the sialylation of a variety of glycolipids (GM3, GD3, and α2,3-sialylparagloboside), was identified as a therapeutic target for glioblastomas [81]. Other ST8Sia family members, such as ST8Sia V and ST8Sia VI, are also related to malignant potential. ST8Sia V, the enzyme adding Neu5Ac to gangliosides, was expressed at a low level and negatively correlated with patient survival in

bladder cancer and colon cancer [82][83]. ST8Sia VI generates disialic acid structures preferentially on O-linked glycoproteins, and these products are proven to bind with Siglec-7 and Siglec-9. Studies have shown that ST8Sia VI contributes to tumor growth in a mouse model by inhibiting immune responses via the alteration of the macrophage polarization towards M2 and increasing the immune modulator arginase in the tumor microenvironment [84].

3. The Function of Sialidases in Tumor Sialylation Regulation

The sialidases and sialyltransferases in cells collectively act to maintain sialylation homeostasis. In tumor cells, an abnormally increased level of sialylation is generally attributed to elevated sialyltransferase activities; however, the role of sialidases in regulating the sialylation levels remains to be addressed.

Mammalian sialidases, NEU1-4, are enzymes with distinct cellular localizations. NEU1, mainly present in lysosomes, is associated with the degradation of sialylated glycans and the recycling of sialic acid. Evidence suggests that the upregulation of NEU1 in cancers may increase the utilization of sialic acid, thus contributing to the maintenance of cell sialylation. NEU1 is highly expressed in various cancers, such as liver cancer [85], pancreatic cancer [86], ovarian cancer [87], and melanoma [88]. However, NEU1 is reported to be expressed at low levels in certain stages of tumors and has been found to remove cytosolic sialic acid modifications and inhibit tumor progression [89][90]. Therefore, the effect of NEU1 on tumors must be comprehensively and dialectically analyzed. NEU2 is located in the cytosol and predominantly inhibits tumor growth. The decrease in NEU2 leads to increased sialylation levels and reduces the stemness-like properties of cancer stem cells [91]. Additionally, NEU2 causes a reduction in α2,6-linked sialylation on the Fas protein, leading to apoptosis in pancreatic cancer [92]. In ovarian cancer cells, the overexpression of NEU2 leads to a significant reduction in α2,3- and α2,6-linked sialylation and induces cellular autophagy by upregulating the expression of ATG5, an essential protein involved in autophagosome formation [93]. NEU3, a membrane sialidase, is essential for the hydrolysis of sialic acid in ganglioside. In colon cancer, the upregulation of NEU3 accumulates lactosylceramide and leads to protection against programmed cell death [94]. NEU4 is located in the ER membrane, mitochondria and lysosomes, and is downregulated in many tumors. NEU4 has been reported to negatively regulate the motility of tumors via the desialylation of CD44 in hepatocellular carcinoma [95], as well as reduce sialyl Lewis antigens to prevent cell adhesion to E-selectin in colon cancer [96]. While the role of sialidases in tumors may vary based on tumor type and status, tumor cells consistently regulate sialidase expression and control sialylation in a way that promotes tumor progression.

Sialyltransferases and sialidases are strictly and dynamically regulated to increase and maintain high sialylation levels, which helps to induce the immunosuppressive status of the tumor microenvironment via interactions with immune cells, thus facilitating tumor survival and growth.

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